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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,757	THORSON ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 23, 2004 is acknowledged. Claims 1-28 have been canceled. Claims 29-91 are pending. All of the amendments and arguments have been thoroughly reviewed and considered. Allowability of claims 29-91 have been withdrawn in view of the new grounds of rejections. Accordingly, Applicant's arguments are deemed moot. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

Previous Objections and Rejections

3. The objection to the specification is withdrawn in view of Applicant's amendment of the specification. The prior art rejections under 35 U.S.C. 102(a) are withdrawn in view of Applicant's cancellation of the claims. The prior art rejections under 35 USC 103(a) are withdrawn in view of Applicant's cancellation of the claims.

Information Disclosure Statement

4. The examiner requested a translation of the references DE 198 58 588 and embodiment of WO 95/32181 cited on the form 1449. It is noted that Applicant do not choose to provide such translation at this time. Accordingly, the references cited above will not be considered by the Examiner. Only the abstract has been considered for WO 95/32181.

New Ground(s) of Rejections

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 29-31, 33, 37, 41, 42, 44-46, 48, 52, 56, 57, 59, 60, 63, 64, 66, 70, 72-74, 76, 80, 82-84, 86 and 90 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al. (Nucleic acids Research, Vol. 28, No. 11, pages e52 (i-v). Regarding claims 29, 44, 59 and 60, Li et al. teaches a process for measuring the activity of a nucleic acid cleavage agent and for detecting a nucleic acid cleavage agent present in a sample, the process comprising: incubating the sample with a probe, the probe comprising (i) an oligonucleotide that forms a stem loop structure, (ii) a fluorophore and (iii) a quencher, wherein the fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; measuring the level of fluorescence of the probe and correlating the amount with the activity of the nucleic acid cleavage agent (page e52 (i) column 2, last paragraph to page e52 (ii) column 1, lines 1-22). Additionally, Li teaches the use of multiple molecule beacon probes having different cleavage in separate reaction vessels (see page e52 ii, col. 1, beginning at the 8th line from bottom of page and figure 2, page e52 iii).

Regarding claims 30, 31, 33 45, 46, 48, 63, 64 and 66, Li et al. teach wherein the nucleic acid cleavage agent is an enzyme and wherein the enzyme is a nuclease or endonuclease (S1 nuclease, Mung Bean Nuclease and Dnase I) (page e52 (ii), beginning at the 5th and 6th lines from the bottom of column 1).

Regarding claims 37, 52 and 70, Li et al. the process wherein the recognition site is located in the single stranded portion of the stem loop structure (page e52 (ii), col. 1, lines 3-5 and Figure 1).

Regarding claims 41, 42, 56 and 57, Li et al. teach wherein the fluorophore and quencher are coupled to the 5' end and 3' end of the probe (page e52 (i), beginning at the 4th through 6th line from the bottom of column 2). Li et al further teach wherein the recognition site is located at a site between the quencher and the fluorophore (see Figure 1, diagram and legend).

Regarding claim 72, Li et al teach a process for evaluating activity of a nucleic acid cleavage agent, the process comprising (a) incubating the nucleotide cleavage agent with a probe in a first set of conditions, the probe comprising: an oligonucleotide that forms as stem loop structure; a fluorophore, and a quencher, wherein the fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; (b) measuring the level of fluorescence of the probe in the first set of conditions; (c) incubating the nucleotide cleavage agent with the probe in a second set of conditions; (d) measuring level of fluorescence of the probe in the second set of conditions; (e) comparing the level of fluorescence of the probe in the first set of conditions to the level of fluorescence in the second set of conditions and correlating the level of fluorescence in the first and second conditions to the activity of the nucleic acid cleavage agent (see page 352, iii, Figure 2 and legend).

Regarding claims 73, 74 and 76, Li et al. teach wherein the nucleic acid cleavage agent is an enzyme and wherein the enzyme is a nuclease or endonuclease (S1 nuclease, Mung Bean

Nuclease and Dnase I) (page e52 (ii), beginning at the 5th and 6th lines from the bottom of column 1).

Regarding claim 80, Li et al. the process wherein nucleic acid cleavage agent cleaves the probe in the single stranded portion of the stem loop structure (page e52 (ii), col. 1, lines 3-5 and Figure 1).

Regarding claim 82, Li et al teach a process for evaluating activity the effectiveness of a nucleotide protective agent, the process comprising (a) incubating the nucleotide cleavage agent with a probe, the probe comprising: an oligonucleotide that forms as stem loop structure; a fluorophore, and a quencher, wherein the fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; (b) measuring the level of fluorescence of the probe as incubated in step (a); (c) incubating the nucleotide protective agent, the nucleotide cleavage agent and the probe; (d) measuring the levels of fluorescence of the probe as incubated in step (c); (e) comparing the level of fluorescence of the probe in steps (b) and (d) and correlating the difference in the florescence levels measured in steps (b) and (d) with the effectiveness of the nucleotide protective agent. In this case the nucleotide protective agent is dNTP(s) (see page e52 iii, figure 2, at (d), and page e52 iv, col. 1, first full paragraph

Regarding claims 83, 84 and 86, Li et al. teach wherein the nucleic acid cleavage agent is an enzyme and wherein the enzyme is a nuclease or endonuclease (S1 nuclease, Mung Bean Nuclease and Dnase I) (page e52 (ii), beginning at the 5th and 6th lines from the bottom of column 1).

Regarding claim 80 and 90, Li et al. the process wherein nucleic acid cleavage agent cleaves the probe in the single stranded portion of the stem loop structure (page e52 (ii), col. 1, lines 3-5 and Figure 1).

Therefore Li et al meets the limitations of the claims 29-31, 33, 37, 41, 42, 44-46, 48, 52, 56, 57, 72-74, 76, 80, 82-84, 86 and 90 of the instant invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 35, 36, 38, 39, 40, 50, 51, 53, 54, 55, 68, 69, 71, 78, 79, 81, 88, 89 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. as previously applied above in view of Battigello et al. (Bioorganic and Medicinal Chemistry, Vol. 3, No. 6, pages 839-849, June 1995). Regarding claims 35, 36, 50, 51,68, 69, 78, 79, 88 and 89, Li et al. teach process

comprising: incubating a sample containing a nucleic acid cleavage agent with a probe, the probe comprising (i) an oligonucleotide that forms a stem loop structure, a fluorophore and a quencher, wherein fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; and measuring the level of fluorescence of the probe and correlating amount of fluorescence when the probe is cleaved; measuring the level of fluorescence of the probe; and correlating amount of fluorescence with activity of the nucleic acid cleavage agent. Li et al also teaches wherein the cleavage agent is an enzyme which cleaves single stranded nucleic acid molecules. Li et al differ from the instant invention in that Li et al do not expressly teach wherein the cleavage agent is a small molecule or wherein the cleavage agent is enediyne. However, Li et al. provides motivation for using other enzymes and/or molecules in the method in the teaching that the method developed here is convenient and accurate in detecting the influences of various catalytic conditions on DNA cleavage. In a general teaching, Battigello et al teach the use of the small molecule enediyne to cleave single-stranded nucleic acid molecules. Battigello et al teach wherein the enediyne compounds exhibit cleavage of an RNA substrate near the 5' end and cleavage in a single stranded loop region of the RNA substrate (abstract). Therefore in view of the foregoing, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that the enediyne et al compounds as taught by Battigello et al could be used in the molecular beacon-based cleavage assay of Li et al. to cleave the hairpin-shaped oligonucleotides based on the teaching of Battigello et al that the enediyne compounds are capable of cleaving single stranded loop regions of a nucleic acid substrate.

Regarding claim 38, 53, 71, 81 and 91, Li et al teach wherein DNAse I is used to cleave the probe in the single-stranded portion of the stem loop structure (the recognition site for the cleavage agent). Li et al further teach that DNase I can digest both single and double stranded DNA and thus the fluorophore and quencher in the molecular beacon should be separated from each other after DNAse I digestion (page e52 (ii), column 2, lines 5-8). Battigello et al discloses wherein enediyne compounds are capable of cleaving nucleic acids in the double stranded and single stranded conformation (abstract and page 843, column 2, lines 14-17). Therefore, it would have been obvious to one of ordinary skill in the art that the nucleic acid cleavage agent as taught by Li et al and Battigello et al cleaves the nucleic acid probe (substrate) in the single stranded and double stranded conformation.

Regarding 39, 40, 54, 55 Battigello et al. disclose wherein the cleavage recognition site spans a junction between the single stranded and double stranded portion of the stem loop structure or is internally in the strands (page 843, figure 4 and page 846, figure 6).

10. Claim 32, 34, 47, 49, 65, 67, 75, 77, 85 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al as previously applied in view of T.A. Brown (Molecular Biology LabFax, Bios Scientific Publishers, Academic Press, Inc., San Diego, CA, 1991, pages 93, 114-125, 139, 154-157 and 163). Regarding claims 32, 34, 47, 49, 65, 67, 75, 77, 85 and 87, Li et al. teaches a process for measuring the activity of a nucleic acid cleavage agent and for detecting a nucleic acid cleavage agent, wherein said cleavage agent is a nuclease or endonuclease present in a sample, the process comprising: incubating the sample with a probe, the probe comprising (i) an oligonucleotide that forms a stem loop structure, (ii) a fluorophore and (iii) a quencher,

wherein the fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; measuring the level of fluorescence of the probe and correlating the amount with the activity of the nucleic acid cleavage agent. Li et al. further teach wherein the recognition site of the cleavage agent is located in the single stranded portion of the stem loop structure and wherein the cleavage agent is a nuclease or endonuclease, such as e.g., DNase I, S1 nuclease and mung bean nuclease. The method Li et al. differs from the instant invention in that the reference does not teach wherein the cleavage agent is a restriction enzyme or an exonuclease. However, Li et al does not exclude the use of restriction endonucleases in the cleavage method, but rather teaches an improvement of using single stranded specific nucleases, such as, e.g., S1 nuclease (pages e52 i and e52 iii).

In a general Labfax manual, T.A. Brown teaches a chapter discussing numerous restriction endonuclease and their recognition sequences. Likewise the reference provides a table which gives inactivation temperatures, effects of salt concentrations, star activities and activities on single stranded DNA (see Chapter 4, especially pages 115 -125). T.A. Brown also discloses in Chapter 5, DNA and RNA modifying enzymes such as nucleases and exonucleases that are specific for single stranded DNA. For example, the reference teaches the endonuclease S1 nuclease which is specific for single stranded DNA as taught by Li et al. and exonuclease 1, which is an *E coli* exonuclease that is specific for single stranded DNA. Therefore, in light of the teaching of T.A. Brown, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that restriction endonuclease or exonuclease comprising the same functional properties as those taught by Li et al. are capable of use in the cleavage method of Li et al with a reasonable expectation of success.

11. Claims 43, 58, 61, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al as previously applied in view of Bruchez Jr. (US 6,500,622 B1, effective filing date March 29, 2000. Regarding claims 43, 58, 61 and 62, Li et al. teach a process for measuring the activity of a nucleic acid cleavage agent and for detecting a nucleic acid cleavage agent as previously discussed above. The method of Li et al differ from the instant invention in that Li et al. do not expressly teach wherein the probes are immobilized on a solid support or wherein the multiple probes comprises different fluorophores and wherein the process comprising multiple probes are carried out in the same reaction vessel. In a general teaching, Bruchez Jr. et al teach wherein probes such as, molecular beacon probes or probes comprising stem-loop structures are attached to a solid support such as, e.g., beads. Bruchez Jr. teaches wherein the probe or probes may be utilized in multiplex formats (same reaction vessels) and wherein multiple labels such as, e.g., fluorophores, may be attached to the different probes. (column 2, lines 41-65, Figures 1-11 and column 6, line 64 to column 7, line 42 and col. 24, lines 44-61). Bruchez Jr et al further teach that the use of polynucleotide attached to a solid support, such as, e.g., beads, is advantageous because it allows large number of different probes polynucleotides and/or target polynucleotides to be simultaneously interrogated (col. 6, lines 24-34). Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the cleavage method of Li et al. to encompass attaching the probes to a solid support, such as beads, as taught by Bruchez Jr et al for the benefits of interrogating multiple polynucleotide cleavage reactions simultaneously as suggested by Bruchez Jr et al.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER

5/7/2004